Design of the Syst-Eur trial and Syst-Eur Phase 2: Thomas Weihrauch's contributions

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On the occasion of the publication of the results of Syst-Eur Phase 2 [1], we wish to pay a special tribute to the pioneers of this trial, the late Professor Antoon Amery, and Professor Thomas Weihrauch.

These two outstanding clinical and pharmacologically orientated scientists happened to meet on a aeroplane back in 1986, soon after the publication of the EWPHE trial [2]. This meeting, where Antoon Amery unfolded his preliminary plan for a new study in elderly subjects with isolated systolic hypertension (later to be named Syst-Eur) received an enthusiastic response from Thomas Weihrauch, and the two of them immediately got down to business. It was agreed that such a (placebo-controlled) study would most likely allow the then new generation of antihypertensive drugs to demonstrate their potential value in preventing hypertensive end-organ damage. This might fill the information gap versus the proven value of diuretics and β-blockers in that regard and, at the same time, provide support for the then questionable concept of treating elderly individuals with isolated systolic hypertension. (The Systolic Hypertension in the Elderly Program, started in the USA, was also intended for the latter purpose but did not include the new-generation drugs).

From a pathophysiological point of view, Amery and Weihrauch both favoured the use of a dihydropyridine calcium antagonist as the first-line active drug regarding elderly hypertensives. Weihrauch added another dimension to their deliberations by referring to a recently published paper in which it was shown that [^{3}H]-nitrendipine in the rat brain preferentially binds to areas that, in man particularly, are affected by Alzheimer's disease: the superficial cortex, thalamus and hippocampus [3]. That feature supposedly might add a specific benefit in elderly hypertensives. Hence, the choice fell on this particular calcium antagonist, as has subsequently been justified in the course of the Syst-Eur substudy on cognitive deterioration [4].

The Syst-Eur project required a large group of participating centres throughout Europe (including Israel), and hence elaborate preparations. The first patients were randomized in 1989, and the protocol was published in 1991 with Professor Antoon Amery as first-named author [5]. As fate would have it, soon afterwards, Antoon fell victim to a progressive and fatal illness, and died in 1994. In that critical episode, he conveyed his co-ordinating task in the Leuven Syst-Eur centre to one of us (J.A.S), withdrawing from further authorship.

Professor Thomas Weihrauch was never identified as an author on any Syst-Eur publication, by his own volition. Because of his formal association with the main sponsor of the trial, he felt it was proper to remain in the background. We respected that, although his enduring loyalty to the investigators, as well as his purely scientific contributions to the evolution of the project over the years, would certainly have entitled him, at least in our view, to a prominent co-authorship.

His devotion to Syst-Eur became particularly decisive in one particular episode when we faced the end of the randomized phase of the trial, which was originally predetermined to be its termination [6]. In that period, we became increasingly worried that our trial population in less privileged European countries might become cut-off from appropriate continuation of antihypertensive treatment after formal closure of the trial, and hence the supply of trial drugs. As a matter of course, this applied particularly to those patients who were randomized to the active treatment arm, but hardly less so to those whose actual treatment requirements deviated from the per protocol purpose of placebo treatment. The ideal solution to this ethical dilemma would be to organize a transition period during which the entire trial population would be offered active trial medication, maintaining the logistics of supply and supervision. In that way, the local

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investigators could extend their current observation and prepare themselves and their patients for long-term routine treatment. Of course, this would be a revolutionary way of taking leave of a trial population in a civilized fashion, but also one which by and large would pose an excessive and unforeseen financial burden on the trial's main sponsoring drug house. Faced with this existential dilemma, Thomas Weihrauch fully rose to the challenge not only by unreservedly sharing our ethical concerns, but also by offering an intellectual and pragmatic rationale on the part of the pharmaceutical industry. He argued that a substantial extension of observation might well provide a unique opportunity to settle once and for all question of a cancer scare and allied warnings in relation to chronic calcium channel blockade, as issued from certain corners [7]. That argument clinched the 'deal' and allowed us to continue [8], and virtually doubled the observation period for our trial population, much to the latter's benefit and the ultimate proficiency of Syst-Eur.

The Syst-Eur investigators owe a warm tribute to Thomas Weihrauch for his unswerving loyalty to the project which he created together with Antoon Amery almost 20 years ago. We feel committed to do so in writing on behalf of the Syst-Eur community, at the risk of embarrassing our friend Thomas' modest personality.

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